A5 cont.

36. The article of manufacture of claim 35, wherein the sialic acid molecules have a concentration in a range of about 0.0 1 mM to about 100 mM.

A6

45. A bone xenograft for implantation into a human comprising a portion of a bone from a non-human animal, wherein the portion includes an extracellular matrix and a plurality of substantially only dead cells, the extracellular matrix and the dead cells having substantially no surface α-galactosyl moieties and having a plurality of sialic acid molecules linked to at least a portion of a plurality of surface carbohydrate moieties on the xenograft,

whereby the portion of the bone is substantially non-immunogenic and has substantially the same mechanical properties as a corresponding portion of a native bone; and

wherein the bone xenograft has been treated with a glycosidase at a concentration within the range of about 100 mU/ml to about 200 mU/ml.

REMARKS

Upon entry of the present amendments, claims 1-48 remain pending. Applicants have amended independent claims 1, 13, 23, 35 and 45 to recite a range of glycosidase concentrations from about 100 mU/ml to about 200 mU/ml. Support for these amendments is found in the specification on page 9, lines 8-9. Applicants have also amended claims 14, 25 and 36 to more clearly recite "0.01 mM".

Attached hereto is a marked-up copy of the claims as amended, showing the changes made. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE". No new matter is added.

35 U.S.C. § 112, SECOND PARAGRAPH REJECTION

The Examiner has rejected claims 14, 25 and 36 for allegedly failing to particularly point out and distinctly claim the sialic acid molecule concentration that the Applicants regards as the invention. Applicants have amended these claims to more clearly recite "0.01 mM". This rejection is now moot and should be withdrawn.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The Examiner has rejected the claims as allegedly being not patently distinct from the claims of U.S. Pat. Nos. 6,231,608; 6,210,440; 6,402,783 or 5,944,755. Applicants have

amended claims 1, 13, 23, 35 and 45 to recite a range of glycosidase concentrations from about 100 mU/ml to about 200 mU/ml. Accordingly, the pending claims claim a different range of subject matter from the claims of the cited patents. The claimed range is similar to the particularly advantageous test conditions identified by the inventors and disclosed in EXAMPLE 2, page 17 of the specification, lines 24-25. Applicants submit that the advantageous claimed range is therefore nonobvious. Applicants respectfully request that this double patenting rejection be withdrawn.

35 U.S.C. § 103 REJECTION

The Examiner has rejected the claims as allegedly being obvious in view of U.S. Pat. Nos. 6,110,206; 5,944,755; 5,782,915 and 5,922,027. Applicants have amended claims 1, 13, 23, 35 and 45 to recite a range of glycosidase concentrations from about 100 mU/ml to about 200 mU/ml. As discussed above, the claimed range is similar to the particularly advantageous test conditions identified by the inventors and disclosed in EXAMPLE 2, page 17 of the specification, lines 24-25. Applicants submit that the advantageous claimed range is therefore nonobvious. Applicants respectfully request that this obviousness rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of preparing a bone xenograft for implantation into a human, which comprises

   a. removing at least a portion of a bone from a non-human animal to provide a xenograft;

   b. washing the xenograft in water and alcohol;

   c. subjecting the xenograft to a cellular disruption treatment; and

   d. digesting the xenograft with a glycosidase to remove substantially a plurality of first surface carbohydrate moieties from the xenograft,

   wherein the glycosidase has a concentration in a range of about ~~1 mU/ml to about 1000 U/ml~~ 100 mU/ml to about 200 mU/ml, and

   whereby the xenograft has substantially the same mechanical properties as a corresponding portion of a native bone.

2. The method of claim 1, further comprising the step of-subsequent to the glycosidase digesting step, treating a plurality of second surface carbohydrate moieties on the xenograft with a plurality of capping moleculesto cap at least a portion of the second surface carbohydrate moieties,whereby the xenograft is substantially non-immunogenic.

3. The method of claim 2, wherein the capping step comprises treating the second surface carbohydrate moieties on the xenograft with the capping molecules having a concentration in a range of about 0. 1 mM to about 100 mM.

4. The method of claim 2, wherein at least a portion of the capping molecules are sialic acid molecules.

5. The method of claim 1, wherein the glycosidase is a galactosidase.

6. The method of claim 5, wherein the galactosidase is an α-galactosidase.

7. The method of claim 1, wherein the cellular disruption treatment comprises freeze/thaw cycling.

8. The method of claim 1, wherein the cellular disruption treatment comprises exposure to gamma radiation.

9. The method of claim 1 further comprising the step of following step c, exposing the xenograft to a crosslinking agent in a vapor form.

10. The method of claim 1 further comprising the step of following step c, treating the xenograft with a demineralization agent to remove substantially minerals from an extracellular matrix.

11. The method of claim 1 further comprising the step of following step c, adding an osteoinductive factor to the xenograft.

12. The method of claim 1 further comprising the step of following step c, adding a binding agent to the xenograft.

13. (Amended) A method of preparing a bone xenograft for implantation into a human, which comprises

a. removing at least a portion of a bone from a non-human animal to providea xenograft;

b. washing the xenograft in water and alcohol;

c. subjecting the xenograft to a cellular disruption treatment;

d. digesting the xenograft with a glycosidase <u>at a concentration within the range of about 100 mU/ml to about 200 mU/ml</u> to remove substantially a plurality of first surface carbohydrate moieties from the xenograft; and

e. treating a plurality of second surface carbohydrate moieties on the xenograft with a plurality of sialic acid molecules to cap at least a portion of the second surface carbohydrate moieties,

whereby the xenograft is substantially non-immunogenic and has substantially the same mechanical properties as a corresponding portion of a native bone.

14. (Amended) The method of claim 13, wherein the capping step comprises treating the second surface carbohydrate moieties on the xenograft with the sialic acid molecules having a concentration in a range of about 0.01 mM to about 100mm.

15. The method of claim 13, wherein at least the glycosidase is a galactosidase.

16. The method of claim 15, wherein at least the galactosidase is an α-galactosidase.

17. The method of claim 13, wherein the cellular disruption treatment comprises freeze/thaw cycling.

18. The method of claim 13, wherein the cellular disruption treatment comprises exposure to gamma radiation.

19. The method of claim 13 further comprising the step of following step c, exposing the xenograft to a crosslinking agent in a vapor form.

20. The method of claim 13 further comprising the step offollowing step c, treating the xenograft with a demineralization agent toremove substantially minerals from an extracellular matrix.

21. The method of claim 13 further comprising the step of following step c, adding an osteoinductive factor to the xenograft.

22. The method of claim 13 further comprising the step of following step c, adding a binding agent to the xenograft.

23. (Amended) An article of manufacture comprising a substantially non-immunogenic kneebone xenograft for implantation in to a human, produced by

a. removing at least a portion of a bone from a non-human animal to providea xenograft;

b. washing the xenograft in water and alcohol;

c. subjecting the xenograft to a cellular disruption treatment; and

d. digesting the xenograft with a glycosidase to remove substantially aplurality of first surface carbohydrate moieties from the xenograft,

wherein the glycosidase has a concentration in a range of about ~~1 mU/ml to about 1000 U/ml~~ 100 mU/ml to about 200 mU/ml, and

whereby the xenograft has substantially the same mechanical properties as acorresponding portion of a native bone.

24. The article of manufacture of claim 23, further produced by subsequent to the glycosidase digesting step, treating a plurality of second surface carbohydrate moieties on the xenograft with a plurality of capping molecules to cap at least a portion of the second surface carbohydrate moieties on the xenograft, whereby the xenograft is substantially non-immunogenic.

25. (Amended) The article of manufacture of claim 24, wherein the capping molecules have a concentration in a range of about 0.01 mM to about 100 mM.

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26. The article of manufacture of claim 24, wherein at least a portion of thecapping molecules are sialic acid molecules.

27. The article of manufacture of claim 23, wherein the glycosidase is agalactosidase.

28. The article of manufacture of claim 27, wherein the galactosidase is an α-galactosidase.

29. The article of manufacture of claim 23, wherein the cellular disruption treatment comprises freeze/thaw cycling.

30. The article of manufacture of claim 23, wherein the cellular disruption treatment comprises exposure to gamma radiation.

31. The article of manufacture of claim 23 further comprising the step of following step c, exposing the xenograft to a crosslinking agent in a vapor form.

32. The article of manufacture of claim 23 further comprising the step of following step c, treating the xenograft with a demineralization agent to remove substantially minerals from an extracellular matrix.

33. The article of manufacture of claim 23 further comprising the step of following step c, adding an osteoinductive factor to the xenograft.

34. The article of manufacture of claim 23 further comprising the step of following step c, adding a binding agent to the xenograft.

35. (Amended) An article of manufacture comprising a substantially non-immunogenic kneebone xenograft for implantation in to a human, produced by

a. removing at least a portion of a bone from a non-human animal to provide a xenograft;

b. washing the xenograft in water and alcohol;

c. subjecting the xenograft to a cellular disruption treatment;

d. digesting the xenograft with a glycosidase <u>at a concentration within the range of about 100 mU/ml to about 200 mU/ml</u> to remove substantially a plurality of first surface carbohydrate moieties from the xenograft; and

e. treating a plurality of second surface carbohydrate moieties on the xenograft with a plurality of sialic acid molecules to cap at least a portion of the second surface carbohydrate moieties,

whereby the xenograft is substantially non-immunogenic and has substantially the same mechanical properties as a corresponding portion of a native bone.

36. (Amended) The article of manufacture of claim 35, wherein the sialic acid molecules have a concentration in a range of about <u>0</u>.0 1 mM to about 100 mM.

37. The article of manufacture of claim 35, wherein the glycosidase is agalactosidase.

38. The article of manufacture of claim 37, wherein the galactosidase is an α-galactosidase.

39. The article of manufacture of claim 35, wherein the cellular disruptiontreatment comprises freeze/thaw cycling.

40. The article of manufacture of claim 35, wherein the cellular disruptiontreatment comprises exposure to gamma radiation.

41. The article of manufacture of claim 35 further comprising the step of following step c, exposing the xenograft to a crosslinking agent in a vapor form.

42. The article of manufacture of claim 35 further comprising the step of following step c, treating the xenograft with a demineralization agent to remove substantially minerals from an extracellular matrix.

43. The article of manufacture of claim 35 further comprising the step of following step c, adding an osteoinductive factor to the xenograft.

44. The article of manufacture of claim 35 further comprising the step of following step c, adding a binding agent to the xenograft.

45. (Amended) A bone xenograft for implantation into a human comprising a portion of a bone from a non-human animal, wherein the portion includes an extracellular matrix and a plurality of substantially only dead cells, the extracellular matrix and the dead cells having substantially no surface α-galactosyl moieties and having a plurality of sialic acid molecules linked to at least a portion of a plurality of surface carbohydrate moieties on the xenograft,

whereby the portion of the bone is substantially non-immunogenic and has substantially the same mechanical properties as a corresponding portion of a native bone; and wherein the bone xenograft has been treated with a glycosidase at a concentration within the range of about 100 mU/ml to about 200 mU/ml.

46. The bone xenograft of claim 45, wherein the portion of the bone has substantially no minerals.

47. The bone xenograft of claim 45, wherein the portion has an osteoinductive factor implanted in an extracellular matrix.

48. The bone xenograft of claim 45, wherein the portion has a binding agent implanted in an extracellular matrix.